Rejection under 35 USC § 103(a)

The Examiner rejected claims 1-19 under U.S.C. 103(a) as being unpatentable over Lohning (US 2002/0034733) in view of Burger et al. (Appl. Microbiol. Biotechnol. (1999) 52:345-353). Applicants respectfully traverse.

A.   Lohning is not available as prior art under §102(e) prior art

Pursuant to MPEP 706(l)(2), Applicant states: At the time the invention of Application No. 10/522,535 was made, Application No. 10/522,535 and Patent No. 6,753,136, previously published as Lohning (US 2002/0034733), were owned by MorphoSys AG.

The Examiner cites Lohning (US 2002/0034733) as prior art available for use under §103(a) non-obviousness. §103(c), however, provides, in relevant part, that subject matter which qualifies as prior art only under §102(e) shall not preclude patentability under this section where the subject matter and the claimed invention were owned by the same person. The present application is a national stage application of PCT/IB03/03681 filed on July 30, 2003, which claims priority under §119(e) from Provisional Application No. 60/399,150 filed on July 30, 2002. See U.S. Patent Publication No. 20060121563. Pursuant to MPEP §706.02 subsection VI(D), the effective filing date of a U.S. application, which claims the benefit under §119(e) to a provisional application, is the filing date of the provisional, July 30, 2002. Lohning (US 2002/0034733) was published on March 21, 2002. This is less than a year before the effective filing date of the present application; accordingly, Lohning is not available as prior art under §102(b). Lohning's §102(e) date is July 20, 2000, the date of the PCT filing. Lohning and the present application, however, were both owned by MorphoSys AG at the time the invention of the present application was made. The assignment of Lohning to MorphoSys AG is recorded at Reel/Frame 013103/0668. The assignment of the present application is recorded at Reel/Frame 016633/0679. As the provisions of §103(c) are satisfied, Lohning (US 2002/0034733) is unavailable in the consideration of non-obviousness under §103(a).

Since Lohning is unavailable in the consideration of non-obviousness, pursuant to §103(c); Burger alone cannot support a rejection of non-obviousness. Withdrawal of the rejection respectfully is requested.

B.   Reconsideration of §103(a) rejection

In the event that the Examiner maintains that Lohning properly is available as prior art against the instant claims, applicants respectfully traverse. Claims 1-19 are rejected under U.S.C. 103(a) as obvious over Lohning (US 2002/0034733) in view of Burger et al. (Appl. Microbiol. Biotechnol. (1999) 52:345-353). The Examiner asserts that Lohning discloses phagemid vectors comprising a prokaryotic promoter, a first nucleic acid sequence encoding an immunoglobulin-presenting polypeptide, a second nucleic acid encoding a first Ig polypeptide and a third nucleic acid encoding a second Ig polypeptide, wherein a first and second associating agent are fused to or comprised within said Ig-presenting polypeptide and the first Ig polypeptide and comprise a cysteine residue, wherein the first and second Ig polypeptide self-associate to form Fabs. The Examiner further states that Lohning does not teach the single, tricistronic vector of the claimed invention, but instead teaches the use of two vectors, one encoding the Ig presenting polypeptide and a bicistronic vector encoding the heavy and light chain of the resulting Fab. The Examiner also states that Burger teaches tricistronic vectors to achieve stable expression of Ig polypeptides for industrial scale production. Finally, the Examiner states that Burger teaches tricistronic vectors that express three polypeptides of interest, two of which are structural Ig polypeptides and one is a selection vehicle.

In order to present a prima facie case of non-obviousness, the Examiner must articulate one of the KSR v. Teleflex rationales outlined in MPEP 2143, or find that the teaching-suggestion-motivation ("TSM") test outlined in MPEP 2143.01 is satisfied, or find that a reasonable expectation of success existed to combine the prior art under MPEP 2143.02. Here, the Examiner argues that it would be obvious to use the vectors described by Burger to express the genes of Lohning because both are concerned with the expression of three different gene products. The Examiner also argues that Burger provides the motivation to use tricistronic vectors in phage display because of the usefulness of Burger's vectors for obtaining stable expression of three gene products. Applicant respectfully traverses.

As the Examiner admits, Lohning fails to describe tricistronic vectors for use in phage display. Burger describes the use of tricistronic vectors, but the combination of Burger with Lohning fails to teach or suggest the instantly claimed invention for the following reasons: 1) Burger's difficulties in predictably expressing only two structural proteins would not have provided the motivation or expectation of success for a person of ordinary skill in the art to attempt the expression of three structural polypeptides; 2) the tricistronic vector of Burger was

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used in a eukaryotic environment, which is totally incompatible with the prokaryotic environment of the present application; 3) Burger's use of the tricistronic vector for a completely different purpose than the present application, the creation of a cell line for large scale production provides no motivation or expectation of success.

1)   Burger's difficulties in predictably expressing two structural proteins provided no motivation or expectation of success to attempt the expression of three structural polypeptides.

Lohning dealt with the expression of three structural polypeptides by using a dual vector system. The dual vector system was used because of the perceived difficulties of expressing multiple polypeptides from one vector. At the time it was thought that a single vector would be overloaded, especially with the use of one promoter, and not provide satisfactory yields. The problem with the dual vector system, however, is that it requires a selection protocol to verify that the phage or phagemid contains both vectors. It is essentially impossible, however, to use a selection protocol for phage display because of the large scale of the library, which includes ~10^{10} phages. In addition, two vectors can be incompatible, which can hinder expression. A dual vector system provided less than desirable display rates, as shown in Tables I and II of the present application. Therefore, a new vector system was needed. Despite the expectation that the above problems would cause a tricistronic vector to provide even lower display rates than the dual vector system (utilizing a dicistronic vector), the use of the tricistronic vector showed unexpectedly high display rates, as shown in Table II. As a result the present application perfected the use of the tricistronic vector for phage display.

The Examiner states that Burger would have motivated a person of skill in the art to use tricistronic vectors in phage display because of Burger's stable expression of three gene products. Burger, however, had great difficulties using a tricistronic vector to predictably express *two* structural polypeptides; accordingly, Burger would not have motivated a person of ordinary skill in the art to use the same vectors to attempt to express three structural polypeptides that must associate upon expression. Because of the difficulties shown in Burger, a person of skill in the art would likely conclude that the tricistronic vector would not be useful to express three gene products in phage display.

The expression products in Burger differ from that of the claimed invention, as Burger's vector led to the expression of only two structural polypeptides, the Ig light chain and Ig heavy chain fusion polypeptide, and one polypeptide, puromycin acetyltranferase (pac), which acts as a selection vehicle. In the article, Burger highlighted the problems associated with tricistronic

vectors as Southern blot analysis showed an extremely variable mRNA copy number (page 348, column 1) and the tricistronic transfectants produced truncated RNA and unusually high molecular weight mRNA (page 348, column 2). In addition, multiple clones, 1-8, 3-1, and 3-3 failed to reveal any protein equivalent to the heavy chain Ig (page 348, column 2). Burger found that only one tricistronic clone was notably productive, clone 3-2 (page 348, column 2). As a result, transfection had to be repeated to produce viable clones (page 348, column 2). The results show that Burger had great difficulty in creating clones that predictably expressed the desired two gene products to form the fusion protein, let alone three structural polypeptides that must self-associate.

Burger's apparent lack of success and the required multiple transfections to identify a suitable cell line would not have motivated a person of skill in the art nor provided a reasonable expectation of success to use tricistronic vectors to express three structural polypeptides.

Phage display differs from the production of cell lines in Burger. In phage display, the phage cannot be evaluated for successful expression and no selection vehicle can be used; therefore, a greater predictability of reliable expression is needed than that provided by Burger. Burger's methods had the ability to evaluate each individual cell line after transfection for its level of expression and to complete multiple transfections as necessary. Since phage display does not allow for either of these quality assurance steps, this low level of predictability would not motivate the use of tricistronic vectors in phage display.

In addition, phage display differs from the application in Burger in that the three structural polypeptides must then self-associate in order to display functional Fabs. Burger was not concerned with the self-association of the expression products as the heavy and the light chains were extracted from the cells as supernatant, and their association could be accomplished at a later time. Therefore, no motivation or reasonable expectation of success was shown by Burger that three structural polypeptides could be reliably expressed and subsequently self-asssociate.

2)   The tricistronic vector of Burger was used in a eukaryotic environment, which is incompatible with the prokaryotic application of the present application.

Burger describes a eukaryotic system using eukaryotic vectors. The present application describes a prokaryotic system. Burger's eukaryotic vectors would not work in a prokaryotic system. For example, if the pac gene in Burger's vector (page 347, Figure 1), was replaced with the gIII gene, which is necessary in phage display, the vector would not work in a prokaryote. Therefore, a combination of the prior art elements of Lohning and Burger would not work in the present application. Much more was done in the present application in order to provide for a successful use of tricistronic prokaryotic vectors in phage display vectors and at the same time overcome the difficulties shown in Burger.

3)   Burger's use of the tricistronic vector for a completely different purpose than the present application provides no motivation or expectation of success.

Burger used a tricistronic vector for a completely different purpose than the present application. Thus, Burger's goal was the production of a high yield, stable cell line. Burger was concerned with the amount of expression, and showed that with a lot of trial and error a cell line could be created that provided a high level of expression of the two structural polypeptides.

Phage display has a completely different goal. Phage display utilizing gIII displays only a handful of Fabs per phage; accordingly, high expression is not the goal. Phage display requires a balanced and equal expression of each of the three structural polypeptides, so that fully functional Fabs are displayed. In fact, the vector used in the present application uses an inducible promoter that is only moderately 'turned on,' providing for a limited amount of expression within the phage. Over expression within the phage could lead to greater expression and display of non-functional dimers and possible interactions with intracellular components that could both prevent the successful display of functional Fabs.

Burger's completely different application with differing goals would not have provided the motivation or a reasonable expectation of success for the use of tricistronic vectors in phage display, where a moderate, balanced level of expression is required.

Rejection under 35 USC §112

The Examiner rejects Claim 16 under 35 U.S.C. 112, second paragraph, as being vague and indefinite in the recitation of "said first, second and secretory signal sequences are prokaryotic signal sequences." The claim has been amended to clarify that "said first, and

second secretory signal sequences are prokaryotic signal sequences." The amended satisfies 35 U.S.C. 112, second paragraph; accordingly, applicants respectfully requests withdrawal of the rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that the application is in condition for allowance. Should the Examiner feel that there are any issues outstanding after consideration of this response, the Examiner is invited to contact the undersigned to expedite prosecution of the application.

The Commissioner is hereby authorized by this paper to charge any fees during the entire pendency of this application including fees due under 37 C.F.R. §§1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-3840. **This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. §1.136(a)(3).**

Respectfully submitted,

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